REMARKS

The above amendments to the above-captioned application along with the following remarks are being submitted as a full and complete response to the Office Action dated March 2, 2004. In view of the above amendments and the following remarks, the Examiner is respectfully requested to give due reconsideration to this application, to indicate the allowability of the claims, and to pass this case to issue.

Status of the Claims

Claims 1 to 8 are pending in this application. Claims 1 - 5 are being amended to more particularly point out and distinctly claim the subject invention. A new claim 8 is being added to recite other embodiments described in the specification. Applicant hereby submits that no new matter is being introduced into the application through the submission of this response.

Nucleotide Sequence Listing

Pursuant to the Notice to Comply, Applicants hereby submit the nucleotide and/or amino acid sequences and the statement concurrently filed. The accompanying sequence listing in computer readable format and statement under 37 C.F.R. §§ 1.821(e) and (f), along with the remarks, are being submitted as a full and complete response to the Notice.

Prior Art Rejections

Claim 1 was rejected under 35 U.S.C. §102(b) as being anticipated by Lockhart et al. (Nature Biotechnology. Vol. 14, pp. 11675-1680 1996; hereinafter "Lockhart"). Claims 2 to 7 were rejected under 35 U.S.C. §103(a) as being unpatentable over Lockhart, in view of U.S. Patent No. 6,528,264 to Pal et al. (hereinafter "Pal"). These rejections have been carefully considered, but are most respectfully traversed.

The present invention as now claimed is directed to a method for displaying results of a hybridization experiment in which a plurality of probe biopolymers ***immobilized*** on a biochip" p. 6, lines 7-8) are hybridized to a sample biopolymer. The method incorporates the steps of

determining information obtained in the hybridization experiment about a hybridization level for each of the probe biopolymers; determining a **probe** similarity score representing a similarity between first probe data on a base sequence of at least one of the probe biopolymers and second probe data on a base sequence of at least one other of the probe biopolymers ("*a similarity score representing the similarity of base sequences between each of the **probe** biopolymers*" p. 6,lines 11-13); and displaying the information about the hybridization level for each of the probe biopolymers together with the probe similarity score, including generating a visually-intuitive graphical representation of the determined hybridization level and correspondingly determined probe similarity score so as to provide at least one of a visual confirmation of similarities between the base sequences of corresponding biopolymers used in the hybridization experiment and a visual indication of unexpected or improper hybridization.

"*In biochips that use longer DNA molecules, such as cDNA, as a probe biopolymer, no effective technique is known that can evaluate the results of hybridization using DNA sequence data* (p. 3, lines 3-6)." The yeast expression analysis conducted by P. Brown's group of the Stanford University (hereinafter "Brown") merely clusters probes so as to display a cluster tree diagram and indicates a hybridization level between a probe ***A*** and a sample ***B*(*probe vs. sample*** p. 4, lines 2-18), but not similarity level between any two probes (***probe vs. probe***). "*No practical approach is known for determining if a probe biopolymer has been accurately hybridized to a sample biopolymer of interest, and accordingly, there is a need for such a method* (p.4, lines 19-22)." As such, the invention is specifically directed to displaying the **probe** similarity score, **probe** biopolymer data and hybridization-level data are displayed side-by-side so to be compared with each other in a manner that is visually easy to understand (p. 5, lines 5-11). The probe similarity score is represented by square patterns having varying color depths, so as to make the displayed image, and consequently the information being represented, more visually intuitive (p. 6, lines 14-19). As shown in the attached explanatory drawing, the invention measures and displays similarity levels between the probes ***A*** immobilized on a biochip, rather than between a probe ***A*** and a sample ***B*** (not directly immobilized on the biochip, but hybridized with the probe ***A***).

Taking Fig. 18 as an example (claim 7), the similarity pattern matrix 901 shows that Probe 1 and Probe 2 have very similar physical DNA sequences but the tree diagram 1001

indicates that the probes have rather different homologous properties from one another (Probe 1 is more closely related to Probe 4). This suggests that the hybridization-level data reflect the physical similarity of the DNA probes 1 & 2, rather than reflects their homologous similarity present in the sample DNA (p. 19, last paragraph). In other words, the sample DNA molecules of the same type bind to two different types of DNA probes 1 & 2 that are very similar to one another, i.e., unintended hybridization or miss-hybridization(p. 2, lines 12-17). Accordingly, the invention "*determines if unintended hybridization has occurred by observing the hybridization-level information in the proximity of the object probe. Also, by selecting the information to be displayed with the similarity score matrix, the verification of the accuracy of the hybridization is possible in wider ranges* (p. 8, lines 4-9)".

Applicants respectfully contend that Lockhart fails to teach or suggest at least "determining a **probe** similarity score representing a similarity between first probe data on a base sequence of at least one of the probe biopolymers and second probe data on a base sequence of at least one other of the probe biopolymers" so as to provide a visual indication of unexpected or improper hybridization according to the invention.

In contrast, Lockhart merely quantitatively relates hybridization intensities of mRNAs, i.e., samples, to arrays of synthetic oligonucleotides, i.e., probes (***sample vs. probe*** p. 1675, left col., lines 5-8; "*RNA concentration*" Fig. 3; "*A total of 21 murine RNAs were detected at levels ranging from approximately 1:300,000 to 1:100.*" Fig. 5), rather than any similarity levels between the probes immobilized on a biochip (***probe vs. probe***). Lockhart does not disclose, teach or suggest at least displaying the "***probe*** similarity score" along with the hybridization levels or intensities as disclosed or claimed for the present invention.

Pal was relied upon by the Examiner to teach displaying intensity of signals with color differentiation and comparing different biochips. However, Pal fails to compensate for Lockhart 's deficiencies since Pal does not disclose, teach or suggest at least displaying the "***probe*** similarity score" along with the hybridization levels or intensities as disclosed or claimed for the present invention. Pal merely uses false color fluorescence imaging to demonstrate the effectiveness of a substrate to retain DNA, hybridize DNA and provide acceptable signal to noise ratio (col. 5, lines 50-54). Different colors are selected in a convention to indicate relative levels

of probe retention and hybridization (col. 6, lines 24-36). Pal does not display the "***probe*** similarity score" along with hybridization intensity of probes with color differentiation

Neither Lockhart nor Pal discloses, teaches or suggests the generating of a visually-intuitive graphical representation of the determined hybridization level and correspondingly determined probe similarity score nor the providing of a visual confirmation of similarities between the base sequences of corresponding biopolymers used in the hybridization experiment or a visual indication of unexpected or improper hybridization. Lockhart by itself does not show or suggest such features, while Pal merely shows a crude mechanism based on false color fluorescence to visually differentiate its results. The combination of these references would fall short of embodying a method having every feature of the present invention as claimed, most especially the features as noted above.

Further, since claims 2 - 7 recite features in addition to those in independent claim 1 that are already not shown by the cited prior art, these same references cannot be used to render obvious the more specific features of dependent claims 2 - 7. Rather, the present invention as a whole is distinguishable and thereby allowable over the prior art.

Although the invention applies general homology analysis, such as Smith-Waterman method or BLAST (p. 3, lines 7 and 11), the invention applies the homology analysis between probes rather than between a probe and a sample to achieve unexpected results or properties. For example, determining and displaying a probe similarity score. As another example, determining if unintended hybridization occurs (Fig. 18). The presence of the unexpected properties is evidence of nonobviousness. MPEP§716.02(a).

> "*Presence of a property not possessed by the prior art is evidence of nonobviousness. In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963) (rejection of claims to compound structurally similar to the prior art compound was reversed because claimed compound unexpectedly possessed anti-inflammatory properties not possessed by the prior art compound); Ex parte Thumm, 132 USPQ 66 (Bd. App. 1961) (Appellant showed that the claimed range of ethylene diamine was effective for the purpose of producing " 'regenerated cellulose consisting substantially entirely of skin' " whereas the prior art warned "this compound has 'practically no effect.' ").*

Although "[t]*he submission of evidence that a new product possesses unexpected properties does not necessarily require a conclusion that the claimed invention is nonobvious. In re Payne, 606 F.2d 303, 203 USPQ 245 (CCPA 1979). See the discussion of latent properties and additional advantages in MPEP § 2145*," , the unexpected properties were unknown and non-inherent functions in view of Brown or Lockhart, since they do not inherently achieve the same results. In other words, these advantages would not flow naturally from following their teachings, since Brown and Lockhart fail to suggest applying homology analysis among probes thereby determining and displaying probe similarity scores.

Applicants further contend that the mere fact that one of skill in the art could apply homology analysis from 'between a sample and a probe' to 'between two probes' to meet the terms of the claims is not by itself sufficient to support a finding of obviousness. The prior art must provide a motivation or reason for one skilled in the art to provide the unexpected properties, such as determining a probe similarity score or determining if unintended hybridization occurs, without the benefit of appellant's specification, to make the necessary changes in the reference device. *Ex parte Chicago Rawhide Mfg. Co.*, 223 USPQ 351, 353 (Bd. Pat. App. & Inter. 1984). MPEP§2144.04 VI C.

Applicants contend that neither Brown, Lockhart, Pal, nor their combination teaches or discloses each and every feature of the present invention as disclosed in independent claim 1. As such, the present invention as now claimed is distinguishable and thereby allowable over the rejections raised in the Office Action. The withdrawal of the outstanding prior art rejections is in order, and is respectfully solicited.

CONCLUSION

In view of all the above, Applicant respectfully submits that certain clear and distinct differences as discussed exist between the present invention as now claimed and the prior art references upon which the rejections in the Office Action rely. These differences are more than sufficient that the present invention as now claimed would not have been anticipated nor

rendered obvious given the prior art. Rather, the present invention as a whole is distinguishable, and thereby allowable over the prior art.

Favorable reconsideration of this application as amended is respectfully solicited. Should there be any outstanding issues requiring discussion that would further the prosecution and allowance of the above-captioned application, the Examiner is invited to contact the Applicant's undersigned representative at the address and phone number indicated below.

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